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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,488	01/15/2004	David G. Gorenstein	UTMB:1019	5963

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,488	GORENSTEIN ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 4, 2007 has been entered.

Response to Arguments

Applicants' arguments regarding the impropriety of the final rejection are moot in view of the RCE filing, which automatically withdraws finality of the previous action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/425,798, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The parent application does not provide support for thioaptamers that mediate gene silencing, including thioaptamers that are siRNAs that mediate gene silencing through a RISC complex, thus the priority date for siRNA thioaptamers as recited in claims 7 and 10-12 and claim 1 to the extent that it embraces the embodiments of claims 7 and 10-12 is January 15, 2004, the filing date of the instant application. If applicant believes that any of the prior applications provide support for this embodiment, it should be pointed out with particularity in the response to this action.

Claim Objections

Claims 1 and 10 are objected to because of the following informalities: in claim 1 the word "is" should be inserted between the words "and" and "between" in the final line. Claim 10 recites that the thioaptamer comprises a portion of a RISC complex. Because it is unknown how a thioaptamer can comprise a protein, it has been assumed that this claim is meant to recite that the thioaptamer is part of a RISC complex as contemplated

in paragraph 9 of the specification and the presence of the word "comprising" is a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for the reasons set forth in rejection of claim 5 in the office action mailed March 16, 2006 and as clarified in the office action mailed November 3, 2006.

Applicants amendments to claim 1 have overcome the indefiniteness rejection against claim 1 and dependent claims, however, claim 37 has not been amended and this claim continues to be interpreted as reciting thioaptamers comprising an α-thio modified nucleotide triphosphate at the 5' end of the oligomer.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for formulation of compositions comprising an isolated thioaptamer and a carrier, does not reasonably provide enablement for a claim to a pharmaceutical composition comprising an isolated thioaptamer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that this rejection may be overcome by removing the word "pharmaceutical" from the preamble of this claim.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claim 37 recites a pharmaceutical composition. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism.

The specification teaches the isolation of thioaptamers to VEE, the synthesis of a thioRNA library and the use of double stranded thioaptamers to inhibit the luciferase gene in cultured cells. The specification does not provide any examples where thioaptamers are used *in vivo* for any therapeutic purpose.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, of record)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments

> within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to use the claimed thioaptamers as pharmaceuticals. The specification provides an example of inhibition of luciferase in HeLa cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism for the purposes of therapy. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results and the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene that results in a therapeutic effect.

The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claim 37 is not enabled.

This rejection may be overcome by removing the word "pharmaceutical" from the preamble of this claim.

Response to Arguments

Applicants argue the present application discusses how to make, characterize and use pharmaceutical thioaptamer compositions and that information such as pharmaceutical composition dosage and concentration may be supplied by the skilled artisan in the field. While it is correct that dosage and concentration may be easily determined relying on the knowledge in the art, the general guidance in the specification regarding how to use a thioaptamer as a therapeutic is not sufficient to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications.

Applicants further argue that Opalinska reference supports the position that the skilled artisan knows that oligonucleotides and thioaptamers are capable of entering the cytoplasm and diffusing into the nucleus thereby exhibiting nuclear localization, quoting a sentence from page 511, states "...oligonucleotides can escape from the vesicles intact, enter the cytoplasm and then diffuse into the nucleus..." This is not persuasive because when this sentence is read in the context of the paragraph in which it appears the skilled artisan would conclude there are major hurdles to overcome before nucleic acids can be routinely and predictably used therapeutically. The sentences immediately prior to that quoted by applicants read as follows:

> Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome–lysosome compartment, in which most of the material becomes either trapped or degraded. Biological inactivity is the predictable consequence of these events. (emphasis added)

Applicants further characterize the Opalinska reference as teaching in the second paragraph of page 504 that "these techniques have been successfully been used both in-vivo and in-vitro". However, it is noted that this quotation is in fact referring to "anti-gene" techniques using triplex forming oligonucleotides. Applicants also quote from page 504, "...these small molecules have the ability to diffuse into the nucleus where they can contact dsDNA..." Again, this sentence is referring to something other than oligonucleotides or thioaptamers that mediate gene silencing, being directed to the polyamide-based "lexitropsins" of Dervan and co-workers.

Applicants further argue that based on the existence of oligonucleotide treatments in clinical trials and FDA approval of one nucleic-acid drug the skilled artisan knows that oligonucleotides and oligonucleotide pharmaceutical compositions may be used as treatments. This is not persuasive because the majority of clinical trials cited in the Opalinska reference are phase I and II, which test only safety, not efficacy. Further, the existence of one nucleic acid drug is not evidence that all nucleic acid drugs are therapeutically effective. While some nucleic acids have proceeded to clinical trials or have been approved for drug use, the rejection is based in part on the lack of a demonstrated therapeutic effect for the particular claimed oligonucleotides and the ability of other nucleic acids to act therapeutically does not lead the skilled artisan to recognize the instantly claimed nucleotides to act as a therapeutic.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 9 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Baracchini (US 5,801,154, of record).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which is the equivalent of a phosphorothioate linkage. Thioaptamer is defined in the specification on page 6 as encompassing antisense oligonucleotides and ribozymes. The thioaptamer may comprise a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer may be fully or imperfectly complementary to the target gene and the silencing can occur through repression of translation, mRNA cleavage or binding to a 3'UTR. The thioaptamers can comprise compositions with a carrier.

Baracchini et al. disclose antisense oligonucleotides that are targeted to and inhibit multi-drug resistance associated protein. These antisense oligonucleotides are 8-30 nucleotides in length, contain phosphorothioate linkages, are comprised of RNA or DNA, are targeted to numerous regions including the 3'UTR and are provided as compositions comprising a carrier (see claims 1 and 4-6 and columns 6-7). At column 3, lines 32-34 Baracchini et al. disclose that antisense oligonucleotides do not have to be 100% complementary to the target gene. It is known in the art that antisense inhibition occurs through an RNAse H mechanism that cleaves mRNA and prevents translation of the mRNA into protein.

Thus, Baracchini et al. disclose all limitations of and anticipate claims 1-4, 6, 8, 9 and 15-17.

Claims 1-4, 6, 7, 9 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

The claimed invention is directed to isolated thioaptamers 15-25 nucleotides in length that mediate gene silencing and comprise one or more ribonucleotide monophosphates, which is the equivalent of a phosphorothioate linkage. In specific embodiments the thioaptamer comprises a 3' OH group and may be composed of ribonucleotides or deoxyribonucleotides. The thioaptamer can silence a gene can occur through mRNA cleavage.

Agrawal et al. disclose self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On pages 15-16 Agrawal et al. disclose the oligonucleotide is a single nucleic acid strand that forms a double stranded structure and the self-complementary region of the oligonucleotide is fully complementary to the hybridizing region to form a duplex. On page 8 Agrawal et al. disclose that the self-stabilized oligonucleotides is composed of ribonucleotides, deoxynucleotides and/or modified nucleotides. At page 14 Agrawal et al. disclose that the oligonucleotide can comprises phosphorothioate linkages. On pages 17, line 27 through page 18 Agrawal et al. disclose that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals.

Thus, Agrawal et al. disclose all limitations of and anticipate claims 1-4, 6, 7, 9 and 14-16.

Claims 1, 7 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell 2000, of record).

The claimed invention is directed to thioaptamers that mediate gene silencing. In specific embodiments the thioaptamer comprises a double stranded RNA fully complementary to a target that silences the gene by mRNA cleavage, is part of a RISC complex, is produced by a DICER complex or is a siRNA.

Parrish et al. disclose double stranded RNAs comprising phosphorothioate linkages that are complementary to and inhibit the *unc-22* gene of *C. elegans* by RNA interference. As evidenced by the post-filing art of Zhang et al. (of record), Dicer is a multidomain ribonuclease that processes long dsRNAs to fragments of 21-25 nucleotides having 3'-OH termini during RNA interference and is part of the RISC complex. Although Parrish et al. are silent as to the cleavage of long dsRNAs into double stranded duplexes 15-25 nucleotides in length having 3'-OH termini, the long dsRNA molecules disclosed by Parrish et al. are necessarily cleaved into such duplexes. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. Inherent anticipation does not require recognition in the prior art. Since Parrish et al. teach phosphorothioate dsRNA and the resultant RNA interference, and it has since been discovered that this effect is mediated

by the activity of Dicer, which cleaves long dsRNA into fragments that are 15-25 nucleotides long, the teachings of Parrish et al. anticipate the instant invention.

Thus, Parrish et al. disclose all limitations of and anticipate claims 1, 7 and 10-12.

Response to Arguments

Applicants traverse the rejection over Parrish by arguing this reference is not prior art with regards to the present application since analogues of RNA having sulphur in place of oxygen as one of the non-bridging ligands bound to the phosphorus were disclosed in the parent application filed on 10/25/1999. This argument is not persuasive because the parent application does not disclose aptamers that mediate gene silencing by RNA interference and thus do not disclose siRNAs that are the subject of claims 7 and 10-12 and claim 1 to the extent that claim 1 embraces the embodiments of claims 7 and 10-12. This was originally stated in the office action mailed 3/16/2006 and is repeated above for applicant's convenience.

Applicants further argue that Parrish fails to disclose and enable every element to the claims, asserting Parrish discloses partially thiomodified phosphodiester backbones having no more than a single modification along the backbone. Applicants note that Parrish states that they "...were able to demonstrate interference activity following the incorporation of a single modified residue" and further limited the single modification to A, G or C residues and conclude that Parrish does not enable the use of partially thiomodified thioaptamers. This is not persuasive because the claims do not require multiple thiophosphates, only partial thiophosphate modification; one thiophosphate

would provide a partially modified oligonucleotide. Additionally, Parrish does disclose the inclusion of multiple phosphorothioates. The experiments were performed by substituting a thiophosphate modified NTP in an enzymatic synthesis (see materials and methods), therefore if the ATP is substituted every A residue in the RNA would be phosphorothioate, not only one A residue.

Applicants further argue Parrish does not disclose thioaptamers of 15-25 nucleotides and does not disclose a thioaptamer having a perfect or imperfect complementarity match to a target gene, This argument is not persuasive because as noted in the rejection, the RNAs of Parrish are necessarily cleaved to RNAs of this size range by DICER (meeting the limitations of claim 11) and Parrish discloses the synthesis of RNAs targeted to unc-22. Applicants note that Parrish teaches that sequence and motifs are unimportant as they "...were able to rule out a specific requirement for any sequence motif in the trigger or target RNA and were able to rule out any requirement for A, U, or C residues in the fragment sequence". The relevance of this argument is not understood because this merely states that RNA interference mechanism does not require a particular sequence motif and provides no evidence that the RNAs of Parrish did not have complementarity to a target.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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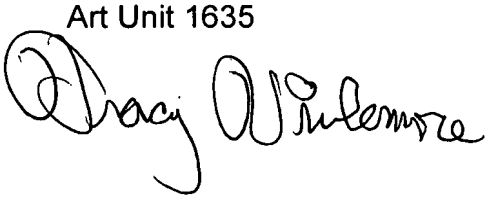
Tracy Vivlemore
Examiner
Art Unit 1635



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